American Journal of Pharmacy

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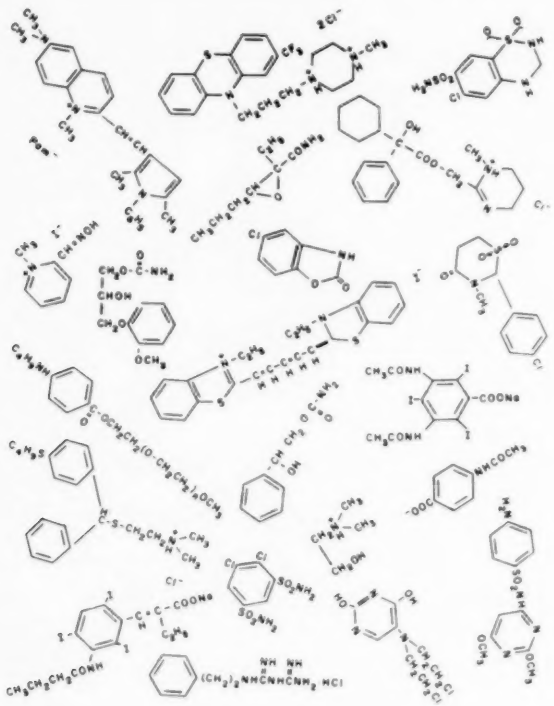

NEW MEDICINALS

See Article "New Drugs of 1958"

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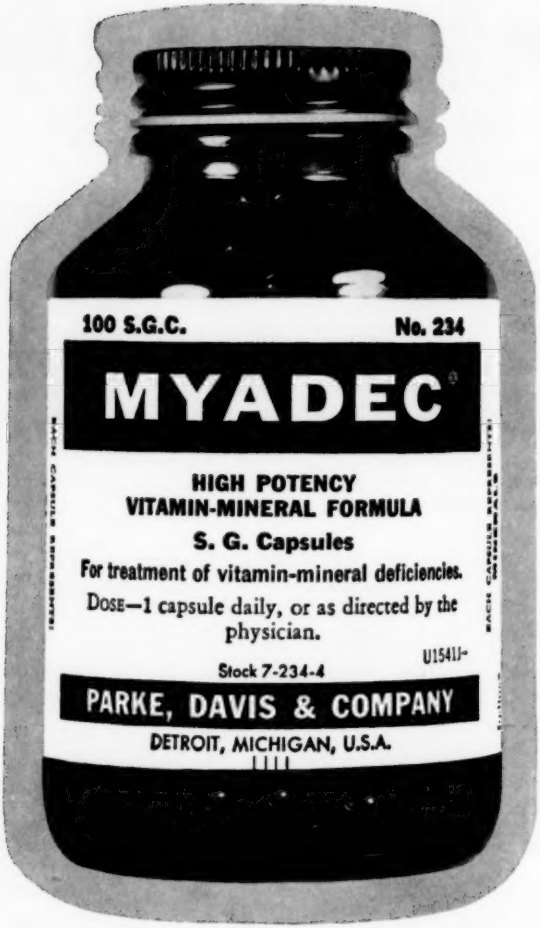

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E D I T O R I A L

AN INDUSTRY PROBLEM

FEW if any industries in the United States spend a higher per cent of sales or profits on research than does the drug industry. This is the source of our industry's rapid progress but it is also the cause of an unbelievably high rate of obsolescence.

Those who believe that no competition exists among drug manufacturers could not be more in error. It would be well if they could see first hand the intense research effort that is expended in the laboratories of every company of any size or stature—effort that is sparked and directed with the certain knowledge that to the successful will go tomorrow's sales, while those who bask in the sun of yesterday's achievements will falter and fall by the wayside.

The drug industry, over the last few decades, has indeed grown but it has not forged ahead through luck or because of the public's preoccupation with matters pertaining to health. The drug industry has amassed truly impressive research facilities staffed by some of the best scientists in the world. With such organized effort, new medical discoveries in the form of a continuing array of wonder drugs and improved dosage forms is inevitable.

While these new and often dramatically effective agents have brought financial growth to the drug industry, this is not their most important aspect. The major contribution and the one which touches every man, woman, and child in this country in the tremendous improvement in the health of our people. Not only does life-expectancy continue to rise but illness and crippling disease become less and less an insurmountable problem in our daily lives. Good health, when it exists, is only too often taken for granted. It is easy to forget the diseases which only yesterday decimated whole populations and made inroads on our children and young people. This saving in human suffering and tragedy cannot be equated in terms of dollars for just what is the life of one's child worth?

Today's research effort is directed largely at the diseases affecting those in the upper age brackets and, in time, we will see dramatic achievements in overcoming cancer, hypertension, coronary disease, and peripheral vascular disorders. Even some of today's drugs, although not ideal or perfect, are of great utility in these directions.

The chief problem facing us is not in developing new medicinal agents. The stage is set for this and they shall be forthcoming, each one better than its predecessors. Our problem is to do a better job of explaining to the public at large that their investment in our products and future is truly a bargain and that we are an industry with a full sense of public responsibility. We must also explain that it is the process of free competition and private enterprise which has made our dramatic achievements possible.

It is only too easy for those gifted with political chicanery to convince voters that medical care including drugs should be "free" and that our present system costs too much. We must not combat this with a show of anger, much as we would like to show it. We must present the facts, for they will do much more to silence our critics. We have indeed accomplished many miracles, and more are to come. We should welcome every opportunity to explain them and why they cost what they do. Indeed, we should seek this opportunity for upon such efforts depends our future status as well as our program and progress in improving the health of all people.

L. F. Tice

NEW DRUGS OF 1958

By L. F. Tice *

During 1958, a wealth of new drugs were released—the results of pharmaceutical and clinical research. The modern practice of medicine is geared to a rapid acceptance of those agents which represent an advance in therapy. Toward this end, the pharmacist must be ready and able to acquaint the physician with new drugs, their properties and uses. It is to assist the pharmacist in this challenging but difficult task that this review is presented.

Anti-Infectives

THE problem of resistant staphylococcic infections continues to be a serious one, in spite of the many measures that are being taken to combat it. Greater attention to aseptic technique, scrupulous cleanliness, the quarantine and isolation of infected patients, and other measures have helped, but effective antibiotic therapy is still the main line of defense. For this reason, each new antibiotic having considerable activity against *Micrococcus pyogenes* var. *aureus* (staphylococci) is of considerable interest for they often prove lifesaving.

Erythromycin, while it has been used for some time, is still effective against some strains of this organism but many of the infections caused by the more resistant "hospital" strains are not influenced by it. Some of the more recent antibiotics such as novobiocin, ristocetin, and oleandomycin are more likely to be effective. The latest antibiotics having a good antibacterial spectrum and one embracing resistant staphylococci are kanamycin and vancomycin.

Kanamycin

Kanamycin resulted from some studies at the National Institute of Health in Japan. These studies were concerned with the investigation of a series of antibiotics derived from actinomycetes which did

* Director of the School of Pharmacy, Philadelphia College of Pharmacy & Science.

not possess marked delayed toxicity. Three such antibiotics—phleomycin, alboverticillin, and kanamycin—were isolated and studied extensively. Of these, kanamycin obtained from *Streptomyces kanamyceticus,* a new species, seemed to offer the greatest promise. Intensive studies with this new antibiotic have shown it to be structurally similar to both neomycin and streptomycin, but not identical. Its complete structure is not yet elucidated but it appears to have two amino sugars glycosidically linked to a hydroxylated base. Kanamycin is quite stable, even in solution, and it can be sterilized by autoclaving.

The antibacterial spectrum of kanamycin is quite broad. In addition to its effectiveness against the tubercle bacillus, it may be used against staphylococci, gonococci, and *B. anthracis,* and in many *E. coli,* Shigella, and Salmonella infections. It is also useful in many urinary tract infections. Kanamycin when given orally acts only in the intestinal tract since, like its close relative streptomycin, it is not absorbed. As in the case of neomycin, it is sometimes given orally to "sterilize" the gut prior to surgery. It has also been found promising in the treatment of typhoid "carriers." For systemic or urinary infections, it must be given by intramuscular injection. The usual dose is 0.25-0.5 Gm. every 6-8 hours. In those infections caused by more resistant organisms, the amount given may be increased to 1.0 Gm. Most infections, other than tuberculosis, are controlled by such therapy within eight days. Drug rash and fever are sometimes observed but the most serious untoward reactions to kanamycin are injury to the eighth cranial nerve and kidney damage. Hearing may be impaired but vestibular disturbances are not as likely to occur. Total deafness has resulted in some patients after receiving a total of 40 Gm. or more of the drug.

The use of kanamycin in resistant staphylococcal infections has proven lifesaving but the drug is also of great importance in refractory cases of urinary tract infections and tuberculosis. In the latter, it should, like streptomycin, be given with PAS. Kanamycin is supplied as Kantrex (Bristol Laboratories), in 0.5 Gm. capsules, for oral use in intestinal infections and, in vials of 0.5 and 1.0 Gm., for intramuscular injection.

Vancomycin

The antibiotic, vancomycin, has been on clinical trial for several years and it has now been released as Vancocin (Eli Lilly). It is

produced by cultures of *Streptomyces orientalis* and it is primarily effective against gram-positive organisms. Vancomycin, like kanamycin, appears to be bactericidal in its action and it is particularly useful against resistant staphylococci. Most strains are sensitive to about 2 mcg./ml. and a single intravenous dose of 500 mg. gives blood levels 2-4 times this concentration. A number of hospitals reserve this antibiotic for use only against resistant staphylococcal infections. The usual adult dose is 500 mg. intravenously every 6 hours or 2 Gm. daily by continuous infusion. Since it is not absorbed from the intestinal tract, it should not be used orally. At very high blood concentrations, it may cause some impairment in hearing but this is not likely in patients with normal kidney function. Thrombophlebitis at the site of injection, fever, and drug rash have occasionally been observed.

The drug is supplied by Lilly in vials containing 500 mg. of the dry sterile powder. This is dissolved in 10 ml. of water for injection and then further diluted with isotonic sodium chloride or dextrose solutions prior to injection.

A New Tetracycline

A new member of the tetracycline family was recently announced. It is demethylchlortetracycline. It is produced by a mutant of *Streptomyces aureofaciens,* the organism which Duggar first used in producing chlortetracycline (Aureomycin—Lederle).

Demethylchlortetracycline differs from chlortetracycline in lacking a methyl group at position 15 on the naphthacene ring. A study of the properties of this new antibiotic has shown it to be more stable toward acid and alkali than tetracycline, more potent against certain microorganisms, and excreted by the kidneys more slowly. Demethylchlortetracycline may prove to be superior to tetracycline clinically since comparable antibacterial effects seem possible with smaller doses.

New Dosage Forms

A number of improved dosage forms of some of the standard antibiotics have been released. The increased blood levels of tetracycline produced by phosphates seem to be still further increased if glucosamine is given with the antibiotic. Glucosamine is a non-toxic sugar amine which apparently increases the absorption of tetracycline

from the intestine. Such a combination is now marketed in the form of capsules as Cosa-Tetracyn (Pfizer).

Erythromycin as the propionate (ester) is claimed to be the best form yet developed for oral use. Blood levels are reported to be 2-4 times as high with this derivative as when erythromycin itself in coated tablets is given. Blood levels are also reported to be achieved faster and to last longer. Erythromycin as the propionate is supplied in 125 mg. and 250 mg. capsules as Ilosone Pulvules (Eli Lilly).

A new injection form of erythromycin for intramuscular use is the ethyl succinate dissolved in a polyethylene glycol. It is supplied as Erythrocin I. M. (Abbott).

The triacetyl derivative of oleandomycin, being stable in gastric acid, gives quicker and higher blood levels than the non-acetylated form. It is supplied as Tao (J. B. Roerig & Co.) and as Cyclamycin (Wyeth) in the form of capsules and for oral suspension.

Combined with the three sulfapyrimidines, it is sold as Taomid (Roerig). Together with glucosamine potentiated tetracycline, triacetyloleandomycin is available as Cosa-Signemycin (Pfizer).

For parenteral use in patients who are unable to take the drug orally, oleandomycin is available as the phosphate for intravenous or intramuscular use. Terramycin for parenteral use is also available now in a new form consisting of a ready-to-inject, chelated magnesium complex.

Glucosamine by itself orally has given some evidence of being effective therapy in schistosomiasis. It is theorized that it blocks the utilization of glucose by the worms infesting the patient without being itself toxic to the human host.

Amphotericin-B and Griseofulvin

The new antibiotic amphotericin-B has been described as a very promising drug in the treatment of the tuberculosis-like fungus disease, blastomycosis. It has been found effective in some cases not responding to 2-hydroxystilbamidine, the only other drug known to be of value in this disease. It is presently available as Fungizone for Infusion (Squibb) and is given intravenously in 5 per cent dextrose as the vehicle.

While griseofulvin has been known as an antifungal antibiotic for a number of years, it is presently showing considerable promise

as an oral drug for the treatment of several dermatophytoses. In clinical tests, it has proven of value in tinea capitis and even in the almost incurable onychomycosis.

Anti-Cancer Antibiotics

Several antibiotics have been reported as promising anti-cancer drugs. Among these are Actinobolin, Mitomycin C, and Streptovitacin A. Actinobolin was isolated and studied by a research team at Parke, Davis and Company. It has a considerable antibacterial spectrum against both gram-positive and gram-negative organisms and, in addition, seems to repress the growth of transplanted experimental cancers. The possible clinical value of this antibiotic in cancer is not yet known. The last two named above were developed in Japan and are presently being evaluated in the United States. Mitomycin C has been prepared in crystalline form and is under study by the National Cancer Institute, and Streptovitacin A has been studied at the University of Southern California School of Medicine.

Tuberculostatic Drugs

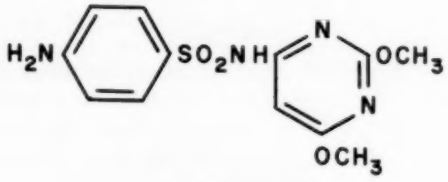
Two new tuberculostatic drugs other than kanamycin are thiocarbanidin (Thioban—Parke Davis) and PAS-Tebamin (Purdue-Frederick). Both are presently on clinical trial. Thioban chemically is 4-isobutoxy-4′-(2-pyridyl) thiocarbanilide. It has given good results in experimental tuberculosis infections and looks promising. PAS-Tebamin is phenyl *p*-aminosalicylate. It seems to be absorbed from the gastro-intestinal tract intact and then split with the release of *p*-aminosalicylic acid in the body. The advantage of the phenyl ester over the free acid is that it is not as disturbing to the stomach and is better tolerated by the patient. It is, of course, as with PAS, best used in conjunction with other therapy such as streptomycin or isoniazid.

Leprosy, like tuberculosis, is caused by an acid-fast, gram-negative bacillus and some tuberculostatic drugs have been tried in this disease. To date, no fully satisfactory antileprotic drug has been developed. Two additions in this field are Dapsone (Alvosulfon—Ayerst) and Ciba 1906. Dapsone is 4,4′-diaminodiphenyl sulfone (DDS) and it is quite similar to the drug sulfoxone sodium (Diasone—Abbott). Sulfoxone sodium is the sodium formaldehyde sulfoxalate derivative of DDS and it is believed to act by the release of DDS in the body.

Dapsone is supplied as 100 mg. tablets. Ciba 1906 has been studied both in the United States and Switzerland. It has been extensively tested by the British Leprosy Research Unit in Eastern Nigeria. Its clinical and bacteriological activity seems good and its non-toxic nature makes it quite suitable for use in children who are both more susceptible to the disease and also less tolerant to other anti-leprotic drugs. Ciba 1906 is a diphenyl thiourea derivative. It not only seems the drug of choice but it may well offer a solution to the problem of leprosy and bring about its control.

New Sulfonamide

A new sulfonamide recently introduced by Roche Laboratories is Madribon. Chemically, it is 2,4-dimethoxy-6-sulfanilamido-1,3-diazine. While it is a close relative of sulfamethazine, it behaves quite differently. Madribon need only be given once a day and it is excreted as the highly soluble glucuronide rather than as the acetylated form. This almost eliminates any likelihood of crystalluria and even the glucuronide has some antibacterial action. The adult dose is 1 Gm. initially, followed by 0.5 Gm. every 24 hours.



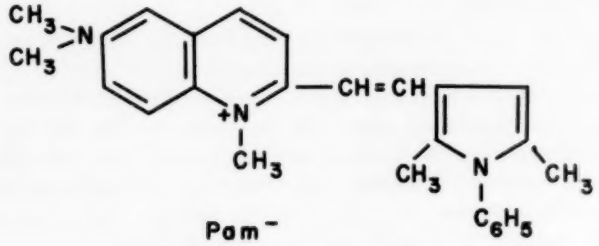
MADRIBON

Madribon is useful in upper respiratory, systemic, and urinary tract infections and it has an antibacterial spectrum similar to that of other sulfonamides. It is available as 0.5 Gm. tablets and as a pediatric suspension. For those cases where a 4 times a day dosage schedule is desired, it is available as Madri*qid* capsules containing 125 mg. each. These require an initial dose of 8; then, 1 four times a day.

The well-known sulfonamide, sulfamethoxypyridazine (Kynex—Lederle) has been prepared in acetylated form for use as a pediatric suspension and it is supplied as Kynex Acetyl Pediatric (Lederle).

Anthelmintics

While piperazine has been a most useful anthelmintic, particularly in roundworm infestation (Ascariasis), any new therapeutic approach in pinworm infestation (Enterobiasis) is of decided interest. A new drug described as effective with a single dose against pinworms (*Enterobius vermicularis*) has been developed by Parke, Davis and Company. It is known as pyrvinium pamoate (Poquil—Parke Davis). Chemically, it is 6-dimethylamino-2[2-(2,5-dimethyl-1-phenyl-3-pyrryl) vinyl]-1-methyl quinolinium pamoate.

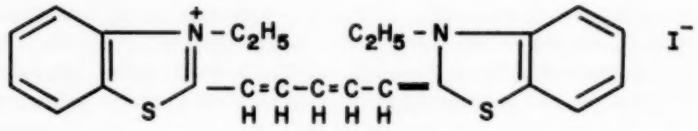


Pyrvinium Pamoate

POQUIL

The most dramatic new anthelmintic is the drug, dithiazanine (Delvex—Lilly). This seems to be the first drug developed that can properly be called a "broad spectrum" anthelmintic since it is effective against a variety of worms infesting man. Dithiazanine is a blue cyanine dye, being chemically 3,3′-diethylthiadicarbocyanine iodide. It is poorly absorbed from the gastrointestinal tract, which is an advantage. This new anthelmintic is effective against roundworms, pinworms, threadworms, and whipworms and is at least partially effective against the dwarf tapeworm, beef tapeworm, and hookworm. Since, in many cases, the patient has a mixed worm infestation, a drug that is effective against several species has a distinct advantage over older drugs that are usually species specific and of no value against others. The adult dose of dithiazanine is 100 mg. three times a day the first day; then, 200 mg. three times daily for 4 more days. In pinworm infestation, 100 mg. three times daily for 5 days may be adequate. In threadworm, a treatment period of 10-14 days may be required with a second treatment period 2 weeks

later. Young children are given about one-half the adult dose. Dithiazanine iodide is available in 50, 100, and 200 mg. enterically coated tablets. It is sold by Eli Lilly and Company as Delvex, Telmid, Partel, and Anelmid in various parts of the world. It is also available as Abminthic (Pfizer).



Dithiazanine Iodide
DELVEX

The treatment of hookworm infestation has always been handicapped by the lack of an effective drug to eradicate this parasite. While tetrachlorethylene is used, it causes considerable nausea and must be followed by a saline purge which is often contraindicated in a patient already dehydrated. For this reason, any new drug showing promise in the control of hookworm is of considerable interest. Recently, such a drug was announced as under intensive clinical investigation by Burroughs Wellcome & Co. It is bephenium hydroxynaphthoate (Alcopara—Burroughs Wellcome). This is a quaternary ammonium compound having the following composition: benzyldimethyl-2-phenoxyethylammonium hydroxynaphthoate. Bephenium seems to be superior to trichlorethylene in its effectiveness and it also eradicates roundworms which are often found associated with hookworms in mixed infestations.

New Biologicals

The use of immune globulin as a means of conferring some degree of passive immunity to certain diseases is a common practice. The gamma globulin fraction of pooled adult plasma contains some antibodies against a number of the diseases affecting children. Adults can be "hyperimmunized" by the injection of a suitable vaccine with an appreciable rise taking place in their antibody level. The globulin fraction of such hyperimmunized adults then becomes particularly

useful to confer a short period of immunity or partial immunity on the person receiving it. Two such new products were recently made commercially available by Hyland Laboratories—Pertussis Immune Globulin and Mumps Immune Globulin. The former is useful in giving a short-term protection to a non-immune child who has been exposed to whooping cough and whose age or physical condition makes the disease hazardous. It may also have some value in minimizing the intensity of the disease after it is contracted. The dose is 1.5 ml. intramuscularly, repeated each week if exposure continues since the possive immunity conferred is of short duration. Mumps Immune Globulin is used to protect children and non-immune adults after exposure. It may also reduce the incidence and severity of orchitis in males who contract the disease after puberty. Its dose is 1.5-4.5 ml., based on body weight, given intramuscularly.

For several years, a combined antigen against pertussis, diphtheria, and tetanus (DPT) has been available, making possible the immunization of children against all three of these diseases. With the development of the Salk poliomyelitis vaccine, experiments were carried out to see if this too might not be combined making possible a single vaccine giving an immunologic response against all four diseases. Two such products have been on clinical trial and are believed to be ready for commercial distribution. They are Tetravax (Merck Sharp & Dohme) and Quadrigen (Parke Davis). Only 0.5 ml. of the product is required for each of the three injections comprising the series. Children under 4 months of age when the series is started should be given a fourth injection.

Intravascular clots are a serious medical problem and the usual anticoagulant drugs, while they can prevent or retard clot formation, cannot dissolve or remove them once they are formed. A new enzyme product, fibrinolysin (plasmin) has been prepared which has marked fibrinolytic action. It is made by activating plasminogen with streptokinase. The latter is an enzyme derived from cultures of hemolytic streptococci. The intravenous use of fibrinolysin causes the dissolution of clots and is of value in phlebothrombosis, pulmonary embolism, cerebral thrombosis, and mesenteric thrombosis. Anticoagulant therapy can be used concomitantly without interference. Fibrinolysin can also be used topically to remove necrotic tissue thereby promoting healing. It is being studied clinically by Ortho Pharmaceutical Corporation.

The enzyme product Varidase (Lederle) is a combination of streptokinase and streptodornase both developed by the growth of hemolytic streptococci. Streptodornase is not dependent in its lytic action on the presence of a plasma factor. It has the property of causing the lysis of purulent material by its action on pus cells (dead leukocytes) while it does not affect living cells. Varidase has been used for some time for its action when applied topically either locally or in suppurating body cavities. More recently, its use intramuscularly has been found of value to reduce inflammation and swelling caused by trauma, and also in such conditions as thrombophlebitis, bronchiectasis, sinusitis, etc. Here, it acts to dissolve the barrier around the traumatized or diseased area permitting a better blood supply to the area and also penetration by any antibiotic carried by the bloodstream. In the event of active infection at the site of injury, it is important to use antibiotic therapy in conjunction with the Varidase since, otherwise, the latter might cause dissemination of the infecting bacteria throughout the body. The most recent product of this type is Buccal Varidase (Lederle). It has been found that this enzyme mixture is absorbed from the buccal sulcus making possible its use by this route rather than by injection. A somewhat similar therapeutic approach is possible using the purified enzyme chymotrypsin obtained from beef pancreas. It, too, causes the dissipation of edema fluid and the absorption of blood clots in traumatized areas. An older product for intramuscular injection is available as Chymar (Armour Laboratories). It is a suspension in sesame oil. A new product is Chymar Aqueous (Armour Laboratories). This is a suspension in isotonic sodium chloride solution. It is given once or more a day in amounts of 0.5-1.0 ml.

The substance heparin is well known for its anticoagulant action in the blood. It is elaborated by the mast cells found in connective tissue surrounding the smaller blood vessels and capillaries from which it is released into the bloodstream. Both the liver and lung tissue are rich in heparin and serve as the source of its commercial preparation. Heparin also acts to clear the blood of lipids and it has an important role in the complex phenomena involved in the transport and utilization of blood lipids. As an anticoagulant, heparin is used parenterally but, recently, it has been found to be absorbed as its potassium salt sublingually. It can be used by this route in doses too small to affect the clotting time but sufficient to clear lipemic

serum. It is presently believed that this use of heparin may give some protection to patients with atherosclerosis and coronary artery disease. The theory is that, by its lipid clearing action, it may retard the progression of the atherosclerotic process and prolong life. These sublingual heparin potassium tablets are available as Clarin (Thos. Leeming & Co.). They are used by allowing one to dissolve slowly under the tongue after each meal.

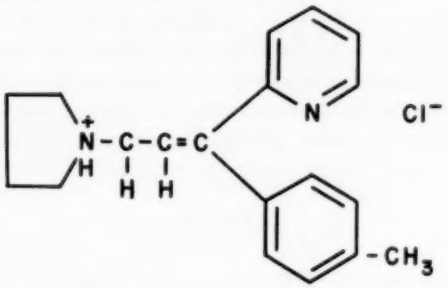
Antihistamines and Antipruritic

During the year 1958, antihistamines continued to be widely used and prescribed. A few interesting new developments can be reported. The very popular and widely used antihistamine chlorpheniramine maleate (Chlortrimeton—Schering; Teldrin—Smith Kline & French Laboratories) has an asymmetric carbon in its structure and, as a consequence, it is a racemic mixture of its two stereoisomers. Schering workers separated these isomers and claim that the dextro form is superior to the levo in antihistamine activity and that it possesses less undesirable side effects. This *d*-form is now marketed as Polaramine (Schering) both as a plain 2 mg. tablet and as a 6 mg. Repetab (Schering).

The drug Trimeprazine (Temaril—SKF), while it is a potent, orally active antipruritic, is very closely related structurally to both the phenothiazine antihistamines and ataractics. Trimeprazine is *dl*-10-(3-dimethylamino-2-methylpropyl)-phenothiazine. It differs from the ataractic drug promazine only in having a methyl group attached to the second carbon of the propyl side chain. It differs from chlorpromazine in having this additional methyl group and lacking a chlorine at position 2 on the phenothiazine nucleus. Trimeprazine has both the properties of an antihistamine and those of a tranquilizer but it is specifically useful in pruritus (itching) regardless of the cause. The usual dose for adults is 2.5 mg. twice a day after meals plus 5 mg. at bedtime. Side effects sometimes observed are drowsiness, dryness of the mouth, and gastrointestinal disturbances. The side effects usually subside after a few days but a central nervous stimulant such as amphetamine may be needed if the drowsiness is too much of a handicap to the patient.

Trimeprazine is sold as 2.5 mg. tablets and as a syrup containing 2.5 mg./5 ml. as Temaril Tablets and Syrup (SKF).

A new, long-acting antihistamine is the drug Triprolidine Hydrochloride (Actidil—Burroughs Wellcome). This is *trans* 1-(4-methylphenyl) 1-(2-pyridyl)-3-pyrrolidino-propene-1 hydrochloride. This drug has a slow onset of action but a long duration probably because of the slow cleavage of the terminal pyrrolidine ring to produce an active compound. It is supplied in 2.5 mg. tablets and as a syrup containing 1.25 mg. per teaspoonful.



Triprolidine HCl

ACTIDIL

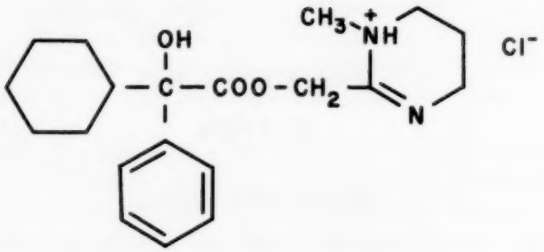
Anticholinergic Drugs

New anticholinergic drugs continue to be added to this already crowded field. One new addition is Valethamate bromide (Murel—Ayerst). This is the methylbromide of the β-diethylaminoethyl ester of phenylmethylvaleric acid. It has the customary therapeutic applications of anticholinergic drugs, being useful in gastrointestinal, genitourinary, and biliary spasm and in peptic ulcer. It is supplied in 10 mg. tablets with and without phenobarbital and also as an injection containing 10 mg. per ml.

Another new drug in this category is ambutonium bromide (Wyeth). It is (3-carbamoyl-3,3-diphenyl-propyl) ethyl dimethyl ammonium bromide and it is a close relative of Isopropamide Iodide (Darbid—SKF). Ambutonium bromide reduces gastrointestinal hypermotility and spasm and it is useful in the management of peptic ulcer and spasm of the gastrointestinal tract. It is supplied as 10 mg. tablets.

The anticholinergic drug Hexocyclium (Tral—Abbott) was introduced in 1957. It is now available in a sustained-release form (Tral Gradumet—Abbott). This is a special non-disintegrating tablet made from an inert plastic matrix. The drug is held within the interstices of the matrix from which it is gradually released after the tablet is swallowed. These sustained-release tablets contain 50 mg. of the drug and the average dose is one, twice a day.

The most recent anticholinergic drug to be released is oxyphencyclimine (Daricon—Pfizer). This, chemically, is 1-methyl-1,4,5,6-tetrahydro-2-pyrimidylmethyl-α-cyclohexylphenylglycolate hydrochloride. Daricon has been reported as giving good to excellent response in patients with peptic ulcer and other gastrointestinal disorders characterized by hypermotility and spasm. Daricon has a long duration of action and needs to be taken only twice daily. It is supplied as 10 mg. tablets.



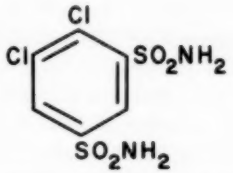
Oxyphencyclimine

DARICON

Diuretics

The use of potent carbonic anhydrase inhibitors in glaucoma is a well-established form of therapy. Both Diamox (Lederle) and Cardrase (Upjohn) are useful for this purpose, acting to reduce the formation of aqueous humor as contrasted with cholinergic drugs which facilitate drainage via the canal of Schlemm. The most recent carbonic anhydrase inhibitor, acting both as a diuretic and to reduce intra-ocular pressure in glaucoma, is dichlorphenamide (Daranide—Merck Sharp & Dohme). This is also a sulfonamide diuretic and has

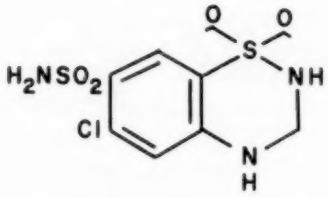
the chemical name 1,3-disulfamyl-4,5-dichlorobenzene. Since it causes some loss of chloride ion as well as bicarbonate ion, it is not as likely to cause a metabolic acidosis as some of the other drugs in this category. Daranide is supplied in 50 mg. tablets and the dose is 25-100 mg., one to three times daily. Daranide is recommended chiefly for use in glaucoma.



Dichlorphenamide

DARANIDE

The sulfonamide diuretic chlorothiazide (Diuril—Merck Sharp & Dohme) introduced in 1957 has been widely used and acclaimed as a most valuable diuretic. While it is a carbonic anhydrase inhibitor, this does not seem to be its only mechanism of action. It seems to be more nearly a true saluretic agent in that Na^+ and Cl^- are excreted in almost equal ratio. In addition, it has some anti-hypertensive action and potentiates other hypotensive drugs such as the ganglionic blocking agents, hydralazine and reserpine. During 1958, the dihydro derivative of chlorothiazide was announced (HydroDiuril—Merck Sharp & Dohme; Esidrix—Ciba). It differs from chlorothiazide only in lacking one double bond and it is believed to be somewhat more potent both in its diuretic and anti-hypertensive action. While it is at present under clinical study, its precise position with respect to possible



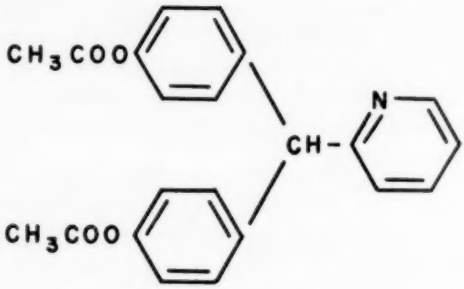
Dihydrochlorothiazide

superiority over chlorothiazide cannot as yet be stated. Meanwhile, the use of chlorothiazide continues to grow and combinations such as chlorothiazide and reserpine (Diupres—Merck Sharp & Dohme) are being released for prescription use.

Laxatives

The wide use and popularity of the anionic surfactant dioctyl sodium sulfosuccinate as a fecal softener and laxative has led to its incorporation with many other laxative drugs. In addition, certain non-ionic surfactants have been used in formulating fecal softeners for their laxative effect. Such a product is poloalkol drops (Polykol Drops—Upjohn). This is a custard flavored solution containing in each ml. 200 mg. of an oxyethylene oxypropylene polymer. The adult dose is 1 ml., 2-4 times daily. It causes gentle fecal softening without irritating the bowel or causing habituation. Polykol Drops are supplied in a 30 ml. dropper bottle.

A new contact laxative is the product bisacodyl (Dulcolax—Geigy). Chemically, this is bis (*p*-acetoxyphenyl)-2-pyridyl methane. Dulcolax is given orally and also used in suppository form. It is not believed to be absorbed but it causes active peristalsis of the large intestine probably by reflex action whether administered orally or applied to the rectal mucosa in suppository form. It is not excreted in mother's milk and does not affect the uterus during pregnancy.



Bisacodyl
DULCOLAX

Dulcolax seems ideally suited for geriatric use, in pregnant women, and nursing mothers. It is supplied as 5 mg. tablets and suppositories containing 10 mg. The tablets require from one to six hours to produce an effect, while the suppositories usually act within about 30 minutes.

Nutritional Products

The atherogenic nature of animal fats and hydrogenated oils seems well established as does the protective action of unsaturated fats. The substitution of unsaturated vegetable oils for animal fats in the diet has been recommended for some time as one means of reducing hyperlipemia and the deposition of lipids as seen in patients with atherosclerosis. Corn oil seems to be particularly suited for this purpose and some workers have suggested that corn oil has some inherent property which protects a person eating it over and beyond that which might be expected by its content of unsaturated fatty acids. Corn oil, while it is quite palatable, is a liquid and many persons prefer a semi-solid margarine-like product as a table spread or shortening. If, however, corn oil were hydrogenated as are cooking fats, its unsaturated characteristics would be lost. Under the name Emdee Margarine (Pitman-Moore), a butter substitute is now available. Its fat content consists of at least 80 per cent non-hydrogenated corn oil but, otherwise, it resembles butter or margarine. This product has an agreeable flavor and taste but it must be kept in a cool place. It is recommended for use both as a table spread and as a kitchen shortening by those who are advised to reduce sharply or eliminate saturated fats in their diet. It is packaged in 1 pound cans.

The possibility of administering fats intravenously has occupied the attention of research workers for several years. There are numerous advantages of fat over carbohydrate for use in the debilitated patient requiring intravenous feeding. Fat provides, gram for gram, over twice the number of calories as carbohydrate or protein. Fats are completely metabolized and are not excreted by the kidneys as is dextrose when the kidney threshold concentration is attained. Fat, not being in solution, does not contribute to the osmotic pressure of the blood and is non-irritating to the venous endothelium.

The earliest fat emulsions, prepared for intravenous use caused rather severe reactions, posed technical difficulties in getting the

particle size small enough to be acceptable, and were difficult to prepare in sterile form. A satisfactory fat emulsion for intravenous use is now available as Lipomul I.V. (Upjohn). It contains 15 per cent cottonseed oil and 4 per cent dextrose, and is emulsified by the use of 1.2 per cent lecithin and 0.3 per cent of an oxyethylene oxypropylene polymer. Most of the oil particles in this oil-in-water emulsion are less than 1 micron and all are less than 5 microns. Lipomul I.V. is indicated in patients suffering from malnutrition and unable to take food by mouth, patients with gastrointestinal diseases accompanied by nutritional depletion, patients with extensive burns, etc. Some few patients have been found to exhibit some reaction during infusion. Such reactions include a "colloid reaction" such as is sometimes seen when other colloids are given intravenously—chill and fever. It is also possible to exceed the patient's tolerance if too much fat is administered thus causing what is described as the "overloading syndrome". This can be quite severe if the administration is not discontinued at once.

With the development of a suitable intravenous fat emulsion, it is now possible to provide all the essential nutrients by this route—carbohydrate, protein (as hydrolysates), fat, and vitamins. Other nutrients, however, should not be mixed with Lipomul I.V. prior to infusion since this may alter its physical form. It is also important to infuse it at a prescribed rate using a special disposable administration unit.

The metabolic defect causing phenylketonuria is a possibility only in children both of whose parents carry this recessive gene. Such afflicted children cannot properly metabolize phenylalanine and the accumulation of ketones in the blood causes mental retardation and eventual imbecility. The only therapeutic approach is to recognize the condition early in infant life and restrict the diet in such a manner that the phenylalanine content is minimal but adequate to meet essential needs. To make this possible, a balanced food formula consisting of a specially processed casein hydrolysate low in phenylalanine, vegetable fat, carbohydrate, vitamins, and minerals is now available as Lofenlac (Mead Johnson). Its use requires careful controls but it does offer a means of providing for the normal growth and mental development of phenylketonemic children.

The absorption of vitamin B_{12}, when given orally, is normally accomplished through the agency of intrinsic factor secreted largely

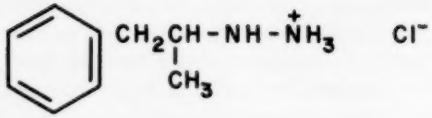
by the gastric mucosa. Increasing the amount of B_{12} given orally is not usually accompanied by any significant increase in absorption unless very large doses are given. It has recently been found that certain polyols, notably sorbitol, act as a B_{12} "absorption enhancement factor" increasing the absorption of orally administered B_{12}. Sorbitol also increases the absorption of orally administered iron. A product utilizing these findings is Vi-Sorbin (SKF). Vi-Sorbin contains pyridoxine hydrochloride, folic acid, vitamin B_{12}, and ferric pyrophosphate in a liquid vehicle which is essentially a saturated aqueous solution of sorbitol. It is not suitable for the treatment of pernicious anemia patients but is recommended as a good source of iron and B_{12} in geriatric, adolescent, and convalescent patients needing a B_{12} and iron supplement.

Two new iron preparations are Chēl-Iron (Kinney & Co.) and Ferronord (Nordson Pharmaceutical Laboratories). The former contains iron in chelated form as iron choline citrate and the latter, a complex between ferrous iron and an amino acid. Both are claimed superior to inorganic iron such as ferrous sulfate when taken orally and to be much less toxic than ferrous sulfate if taken in large overdose. Chēl-Iron is available as both tablets and Pediatric Drops and Ferronord, as tablets.

Psychotropic Drugs

Research in the field of tranquilizers and psychic energizers continued unabated in 1958 with a number of significant developments. The unusual therapeutic properties of iproniazid (Marsilid—Hoffman-LaRoche) coupled with the finding that it is a potent monamine oxidase inhibitor led to an intensive search for new compounds having a similar action. Monamine oxidase inhibitors are believed to function by permitting the accumulation of the neurohormones, serotonin and nor-epinephrine, in the brain with an "energizing" or stimulating action resulting. Several new monamine oxidase inhibitors were announced in 1958. Among these were Catron (JB-516) and Ditran (JB-392), developed by Lakeside Laboratories; RO-4-0831 by Hoffmann-LaRoche; and Phenelzine (W-1544), announced by Warner-Chilcott.

Catron is 1-phenyl-2-hydrazinopropane. It is about ten times as effective as iproniazid and it seems to pass the blood brain barrier

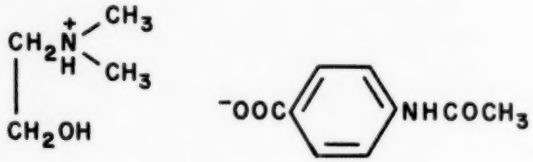


CATRON- JB-516

much more readily. This permits it to act more selectively in brain tissue and minimizes its monamine oxidase activity in the liver. This is probably the reason it appears to be much less toxic than iproniazid. Catron is used in a wide variety of depression states and in relieving anginal pain; it has even been suggested that it is of value as an adjunct in improving a person's adaptation to stress.

Ditran is N-ethyl-3-piperidyl cyclopentylphenyl glycolate hydrochloride. It acts in quite a different way in that it is a powerful hallucinogen or psychotomimetic. It precipitates a bizarre psychological episode lasting about 24 hours. During this time, the patient has hallucinations, becomes disoriented, and loses contact with his environment. This is followed after recovery by a personality improvement which often lasts for a considerable time. Ditran is still under clinical investigation but it appears to have possible value in severe depression states.

A much less potent central stimulant used for somewhat the same indications as amphetamine sulfate is the drug deanol (Deaner—Riker). This is 2-dimethylamino-1-ethanol *p*-acetamidobenzoate (salt). Deaner is believed to act as an acetylcholine precursor, thus improving brain function and increasing alertness. It is slow in exert-

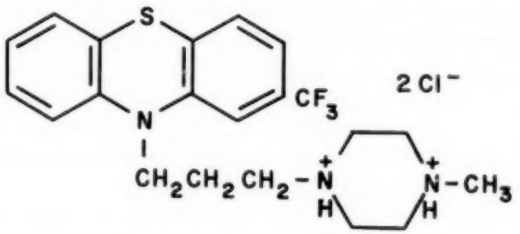


Deanol
DEANER

ing its effect and does not produce the immediate response seen with the amphetamines. It is useful chiefly in mild depression states and fatigue. Deaner is contraindicated in grand mal epilepsy but useful in the psychomotor type. The dose as a central stimulant is 25-75 mg. and it is supplied as 25 mg. tablets.

Another central stimulant recently released is the drug Levonor (Nordson). This is amphetamine combined with alginic acid. It is used for the same general purposes as amphetamine sulfate—as a central stimulant and anorexiant. Since it is used as the alginate, it may have a somewhat more prolonged effect by reason of delayed absorption.

The tranquilizers have continued to be employed quite widely both by the general practitioner and the neuropsychiatrist. There have been several new additions in this field. A newcomer among the phenothiazine derivatives is trifluoperazine (Stelazine—Smith Kline & French Laboratories). This chemically is 10-[3-(1-methyl-4-piperazinyl)-propyl]-2-trifluoromethyl phenothiazine dihydrochloride. It differs from the drug Compazine (SKF) only in having a trifluoromethyl group ($-CF_3$) attached at position 2 on the phenothiazine ring in place of a chlorine. This change, however, greatly potentiates it, the drug being more active than even chlorpromazine (Thorazine—SKF). Stelazine is recommended primarily for patients with frank psychoses rather than in milder cases. It improves both depressed and withdrawn patients as well as those who are overactive and difficult to control. In many cases, it has proven of value when

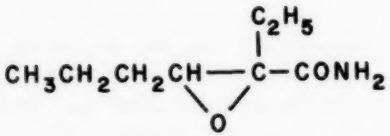


Trifluoperazine

STELAZINE

other drugs have failed. Side effects include extrapyramidal symptoms, motor restlessness, and—in overdosage—hypotension. As with most phenothiazine derivatives, the action of epinephrine is reversed. As a consequence, if blood pressure must be raised, nor-epinephrine must be used. The dose of Stelazine must be regulated to the patient's need. The initial dose is 2 mg. t.i.d. but most patients require about 15 mg. daily in divided doses. It is supplied in 2, 5, and 10 mg. tablets and as an injection for intramuscular use containing 2 mg./cc.

A new tranquilizer somewhat related to the substituted propanediol group is the drug Oxanamide (Quiactin—Wm. S. Merrell). This chemically is 2-ethyl-3-propyl glycidamide. It is employed in much the same way as meprobamate to which it bears some structural similarity. Quiactin is claimed to be superior to meprobamate and to not impair judgment or motor efficiency. It is supplied as 400 mg. tablets.

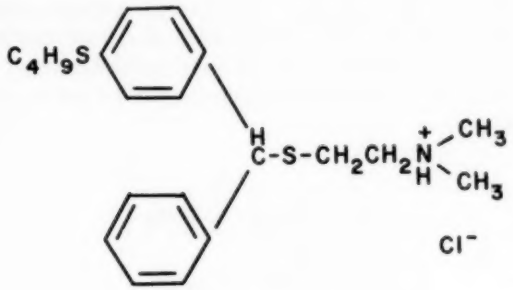


Oxanamide
QUIACTIN

The drug hydroxyzine is a well-known tranquilizer sold under the proprietary name of Atarax (Roerig). This same drug is now available as the pamoate for oral use under the name Vistaril (Pfizer). It is supplied in 25, 50, and 100 mg. capsules. For injection purposes, the hydrochloride is used and it is available in 10 cc. vials containing 25 mg./cc. The therapeutics of Vistaril and Atarax are the same except that Vistaril may have a longer duration of action when taken orally since the pamoate is not very soluble.

Another diphenylmethane derivative is the tranquilizer captodiamine (Suvren—Ayerst Laboratories). This is *p*-butylmercaptobenzhydryl-β-dimethylaminoethylsulfide hydrochloride. It is supplied in 50 and 100 mg. tablets. Suvren is claimed to calm the patient

without causing drowsiness and even to accelerate reaction time and improve concentration.

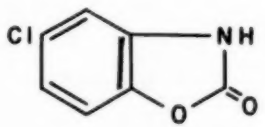


Captodiamine

SUVREN

Muscle Relaxants

Several new muscle relaxants were introduced in 1958. The success of the drug zoxazolamine (Flexin—McNeil Laboratories) led to the study of other related compounds. Such a new drug is chlorzoxazone (Paraflex—McNeil). This is 5-chlorobenzoxazolinone; whereas, Flexin is 2-amino-5-chlorobenzoxazole. The latter has an amino group at position 2 on the ring while Paraflex has an oxygen. Paraflex is used for the same therapeutic purposes as Flexin; namely, in muscle spasm, traumatic pain, fibrositis, etc. It is supplied in 250 mg. tablets. In passing, it should be mentioned that

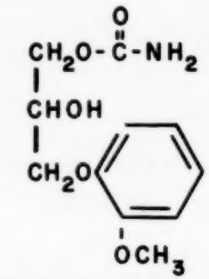


Chlorzoxazone

PARAFLEX

Flexin has been reported to possess a marked uricosuric action. This could be of considerable importance, particularly in gouty arthritis and other conditions associated with high blood urate levels.

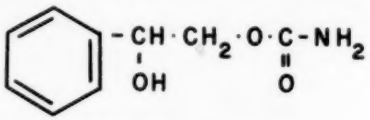
Another muscle relaxant recently released is methocarbamol (Robaxin—A. H. Robins). Robaxin is 3-(*o*-methoxyphenoxy)-2-hyroxypropyl-1-carbamate. It differs from mephenesin carbamate only in being an *o*-methoxyphenyl derivative instead of an *o*-methylphenyl derivative.



Methocarbamol

ROBAXIN

Another muscle relaxant closely related to mephenesin is the new drug Styramate (Sinaxar—Armour Laboratories). Chemically, this is 2-phenyl-2-hydroxyethyl carbamate. It is supplied in 200 mg. tablets.

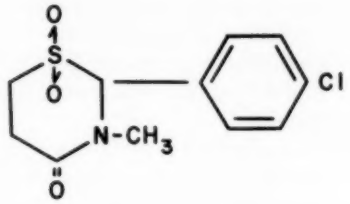


Styramate

SINAXAR

Still another muscle relaxant which also has some considerable tranquilizing action is the drug chlormethazanone (Trancopal—

Winthrop Laboratories). This is 2-(*p*-chlorophenyl)-3-methyl-4-metathiazanone-1-dioxide. This is believed to act in the subcortical centers, the brain stem, and spinal polysynaptic pathways. It has a non-hypnotic central relaxant action and also acts as a tranquilizer. Thus, in addition to its use in various musculoskeletal conditions, it is of value in anxiety states, dysmenorrhea, spastic colon, etc. It is supplied in 100 mg. capsules and the dose is one, 3 or 4 times daily.



Chlormethazanone

TRANCOPAL

Adrenal and Sex Steroids

The search for more potent glucocorticosteroids continued unabated during 1958. The success of prednisone and prednisolone led to the development and release in 1957 of 6α-methyl prednisolone (Medrol—Upjohn) and triamcinolone which is 16-hydroxy-9α-fluoroprednisolone (Aristocort—Lederle; Kenacort—Squibb). The latest potent glucocorticosteroid is 16α-methyl-9α-fluoroprednisolone. This is available as Decadron (Merck Sharp & Dohme) and Deronil (Schering) and is known under the generic name dexamethasone. Dexamethasone is claimed to be 30 times as potent as hydrocortisone and six times as potent as prednisolone. In therapeutic doses, dexamethasone appears to cause no sodium retention, hyperglycemia, or any of the other side effects usually found with adrenal steroid therapy. It is supplied in 0.75 mg. tablets as Deronil (Schering) and in both 0.5 mg. and 0.75 mg. tablets as Decadron (Merck Sharp & Dohme).

Other steroids are also under clinical investigation such as the 16 β-methyl, the 6α-chloro, the 6α-fluoro, and the 6α,9α-difluoro

derivatives. The latter is claimed to be 400 times as potent as hydrocortisone. Such potencies must, of course, be considered rationally since it is not at all certain that beyond a certain point increased activity may provide a therapeutic advantage.

The acetonide of triamcinolone has been found to be superior to hydrocortisone for topical use. The comparison was made in lotions, creams, and ointments wherein only 0.1 per cent of this triamcinolone derivative was used as compared with 1 per cent hydrocortisone. It has been shown not to cause sodium or water retention and to rarely cause irritation or sensitization.

Triamcinolone acetonide is distributed as Kenalog Lotion, Ointment, and Cream (Squibb) and as Aristocort Cream (Lederle). All are 0.1 per cent in strength.

The potentiation of steroids by the introduction of fluorine at the 9α position is also seen in the case of fluoxymesterone (Halotestin—Upjohn). This is 9α-fluoro-11β-hydroxy methyltestosterone. It was introduced in 1957 as an androgen having about 5 times the potency of methyltestosterone. Recently, a combination of 1 mg. of Halotestin and 0.02 mg. of ethinyl estradiol was placed on the market as Halodrin (Upjohn). This balanced combination of orally potent androgen and estrogen seems ideally suited for the management of the menopause, the male climacteric, and osteoporosis which is a frequent complication of aging in both sexes. The administration of androgen-estrogen combinations has become a popular practice in geriatrics in recent years since it causes a positive nitrogen balance, improved muscle mass and tone, and a sense of well-being. It also acts as a prophylactic measure in osteoporosis and even improves those cases advanced to the stage of intense bone pain.

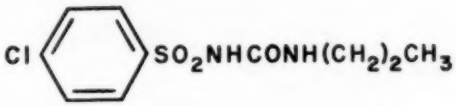
A potent new progestin has also recently been announced. It is 6α-methyl-17α-acetoxyprogesterone (Provera—Upjohn). This was developed following the observation that the 6α-methyl derivative of prednisolone greatly increased its glucocorticosteroid activity. This led to the preparation of 6α-methyl progesterone derivatives to see if their progestational activity would be similarly increased. Provera, orally, is claimed to be more than 100 times as active as Ethisterone. It is used for the same therapeutic purposes such as threatened abortion, etc., and, like other very potent progestins, will when properly used even suppress ovulation.

Antidiabetic Drugs

The clinical success of tolbutamide (Orinase—Upjohn) in the control of many cases of diabetes mellitus has been a great stimulus to research in this field. Tolbutamide is believed to act by stimulating insulin production in the beta cells of the islets of Langerhans. In severe diabetes where more than 40 units of insulin a day are needed, it cannot as a rule be employed in place of insulin.

An interesting application of tolbutamide is its injection as a sodium derivative as a diagnostic test for diabetes. In normal persons, a sodium tolbutamide injection causes a rapid decline in blood sugar levels while in diabetics the decline is much more gradual. This tolbutamide response test requires only 30 minutes while the standard glucose tolerance test requires 2 or 3 hours.

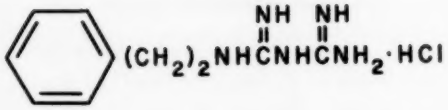
Another oral antidiabetic drug was released in 1958. It is the drug chlorpropamide (Diabinese—Pfizer). This is 1-propyl-3-(*p*-chlorobenzenesulfonyl)urea. It differs from tolbutamide only in having a chlorine in place of a methyl on the ring and one carbon less in the alkyl group attached to the urea nitrogen. Diabinese is claimed to be 2 to 3 times as potent as Orinase, to be longer acting, and to give a satisfactory response in many patients in whom Orinase cannot be used. It is supplied in 250 mg. tablets.



Chlorpropamide

DIABINESE

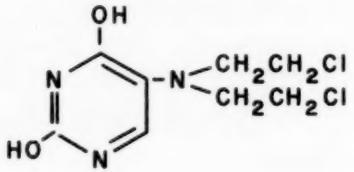
Several other drugs are in the latter stages of clinical trial. One of these is phenformin (DBI—U. S. Vitamin Corporation). This is β-phenethylformamidinyliminourea hydrochloride. Another is metahexamide which is being studied by both Eli Lilly & Co. and Upjohn. Metahexamide is 3-amino-4-methylbenzenesulfonylcyclohexylurea. This, too, is longer acting than tolbutamide and requires a maintenance dose of only 50 to 150 mg. a day.



Phenformin (DBI)

Antileukemic and Anticancer Drugs

While mention was made earlier of certain antibiotics having some anticancer activity, other drugs have been developed recently having considerable anti-tumor activity. One such drug developed by Upjohn is U-8344 which is 5-bis(2'-chloroethyl) aminouracil. This has given very promising results in various experimental rat and mouse tumors and leukemias such as Walker 256 carcinoma, Murphy Sturm lymphosarcoma, Shay myelogenous chloroleukemia, Sarcoma 180, and others. This compound is also of interest since it does not appear to be highly toxic to normal tissue and it can be given orally.



U-8344

Another compound is U-7824 which is N,N-bis(2-iodoethyl)-*p*-aminobenzyl phosphate which, like U-8344, is chemically related to the class of nitrogen mustards. Both U-8344 and U-7824 are much less toxic than most members of this series. Still another anticancer drug under study is 5-fluorouracil which acts by interference with ribonucleic acid synthesis.

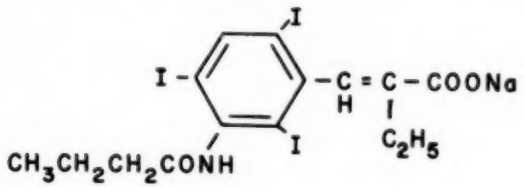
Still another anti-tumor drug under investigation is Degranol developed by the Pharmaco-Industrial Research Institute in Hungary.

This is 1,6-bis(β-chloroethylamino)1,6-desoxy-D-mannite dihydrochloride. It has proven very good in chronic myeloid leukemia and lymphosarcoma and, most important of all, it seems to inhibit metastases in carcinoma.

Diagnostic Aids

Considerable progress has been made in recent years in the development of new contrast media for the X-ray visualization of the biliary and renal tracts. These newer agents are more effective and cause fewer of the side effects such as nausea and dysuria which were so common with earlier drugs in this category.

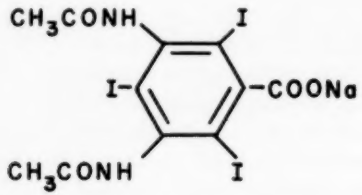
A new agent for use in cholecystography is sodium 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethyl acrylate (Orabilex—E. Fougera & Co., Inc.). This new agent is given orally in a dose which is the same for all patients regardless of weight. It is rapidly absorbed, secreted in the bile, and concentrated in the gall bladder. Its excretion is then largely by way of the kidneys so that intestinal opacities do not interfere with the interpretation of the X-ray films of the biliary tract. The diagnostic dose is 6 capsules, each containing 0.75 Gm. of the drug. They are taken 12-14 hours before the examination is to be made.



ORABILEX

Another contrast medium used in retrograde pyelography is Retrografin (Squibb). This is a 30 per cent solution containing a combination of sodium and methylglucamine diatrizoates, plus 2.5 per cent neomycin sulfate. It is used for retrograde pyelography, thus the addition of neomycin sulfate as an antibacterial agent. This same material, without the neomycin sulfate, is the basis of a product for the delineation of the gastrointestinal tract. It is supplied as Gastro-

grafin (Squibb) and it consists of sodium and methylglucamine diatrizoates in a lemon flavored vehicle to which a surfactant, Polysorbate 80, has been added to improve its penetration into the mucosal folds. It can be administered, following proper dilution, either orally or by enema depending upon which part of the tract is to be visualized. Patients having a history of iodide sensitivity should carry out a buccal sensitivity test before taking it in any quantity.



Sodium diatrizoate

A third product utilizing this same radiopaque agent is Duografin (Squibb). When given intravenously, it permits the visualization of both the biliary and renal tracts. This is particularly desirable when a differential diagnosis must be made between acute renal and acute biliary disease. Duografin is supplied in 50 cc. vials.

The selection of a suitable antibiotic for the treatment of an acute infection is done empirically in many instances. It is far better, however, to know which of the many antibacterial agents are effective against the specific organism causing the infection. A new diagnostic kit called Medikit (Media, Inc.) makes such a determination an easy and simple process. Each Medikit contains 6 Mueller-Hinton disposable Blood Agar Plates, 12 sterilized cotton-tipped applicators, 6 sensitivity record forms, and 6 antibiotic-sulfonamide sensitivity rings. All the physician need do is to streak the blood agar plate with an applicator contaminated with an exudate or mucosal secretion, fit the sensitivity ring on the plate, cover, seal, and incubate. Examination of the plate 12-24 hours later for clear zones will show which of several antibacterial agents may be expected to control the infection. The cost per patient is only $1.25 for each disposable unit.

A combination "dip and read" test strip is now available to detect both glycosuria and proteinuria. The two test areas on the strip are separated by a barrier so that they can be read separately by com-

paring each with the proper color standards. This combined test strip is available as Uristix Reagent Strips (Ames Co., Inc.).

Serological testing for the diagnosis of syphilis is now made easier and more reliable by the availability of a new sensitive protein antigen. This is the new product Ryprogen (Organon). Ryprogen is a highly purified, serologically lipid-free protein antigen extracted from the Reiter strain of *Treponema pallidum*. It can be used in all the different complement fixation tests for syphilis and it has shown excellent sensitivity and specificity. It is supplied in lyophilized form in 10 cc. ampuls. Each ampul provides enough antigen when restored to carry out a large number of tests, the exact number depending on the specific test selected.

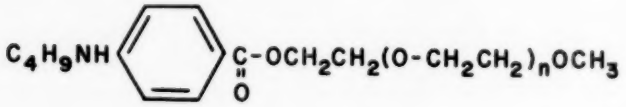
Miscellaneous Drugs

A number of new drugs or new therapeutic applications not described in the several categories already presented are worthy of mention. Considerable interest has been shown the new drug methoxsalen (Meloxine—Upjohn). This, when taken orally a few hours before exposure, promotes tanning and also provides a means of treating patients with vitiligo. This disease is characterized by patches of depigmentized skin. Meloxine was developed as a result of the study of the Egyptian plant *Ammi majus* Linn. which has been used for centuries by the Arabians for vitiligo. Its active principle was found to be 8-methoxypsoralen. This was prepared and studied clinically. The oral administration of the drug in very carefully controlled dosage followed by equally controlled exposure to sunlight or ultraviolet radiation as to time and intensity will cause pigmentation of the skin. It is imperative in using this drug that the dosage and exposure be carefully regulated, and an exposure guide has been made available for this purpose. Meloxine is supplied as 10 mg. tablets and, since the drug is not without some hazards, it should be used only under medical supervision. It can cause some gastric disturbance and, if improperly used, may be toxic to the liver.

A new anticoagulant related to dicoumarin was recently released. It is phenprocoumon (Liquamar—Organon). Chemically, this is 3-(1′-phenylpropyl)-4-hydroxycoumarin. It is claimed to be more potent and to have a shorter latent period before depressing blood prothrombin than its close relatives. It is supplied as 3 mg. tablets.

A drug claimed to be superior to epinephrine in acute attacks of asthma and in patients having both asthma and cardiovascular disease has been announced. It is a close relative of epinephrine being 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol (Bronkephrine—George A. Breon Co.). Bronkephrine is injected intramuscularly or subcutaneously and it usually gives relief in 1 to 5 minutes. Its most important advantage over epinephrine is said to be its lack of pressor action and a much lesser degree of other side effects.

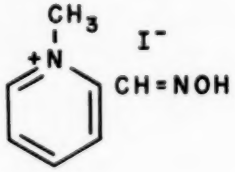
A new anti-tussive drug, benzonatate (Tessalon—Ciba Pharmaceutical Products) is ω-methoxy-polyoxyethyleneethyl *p*-butylaminobenzoate. It is said to act both on the stretch receptors in the lungs as well as on the medullary center involved in the cough reflex. Tessalon is claimed to be non-addicting and not to cause respiratory depression. It is available in capsules containing 100 mg. The dose is one capsule 3-4 times daily. Since as might be expected from its chemical structure it has local anesthetic properties, the capsules should not be chewed.



Benzonatate

TESSALON

The usual antidote to the agricultural insecticide parathion is atropine since parathion, an organic phosphorus insecticide, is a powerful cholinergic poison. PAM, pyridine 2-aldoxime methiodide,



PAM

was recently announced as a valuable antidote for parathion. Developed originally at Columbia University and tried clinically in Japan, it is available in research quantities from Dajac Laboratories, the Borden Chemical Co.

The National Institutes of Health recently announced a new potent analgesic estimated to be about ten times as potent as morphine. It is given the code designation NIH-7519. Chemically, it is somewhat related to morphine but has one less ring system. It is 2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide. This new synthetic seems to be less addicting and to cause less respiratory depression in addition to its increased potency as compared with morphine.

A new non-depressant, rapidly acting anesthetic was recently described. It is 1-(1-phenylcyclohexyl)-piperidine hydrochloride (Sernyl—Parke Davis). Sernyl is used intravenously in a manner similar to the ultra-short-acting barbiturates.

Finally, the antimalarial drugs continue to be reported of value in many conditions totally unrelated to malaria. The successful use of Quinacrine (Atabrine—Winthrop) and Chloroquin (Aralen—Winthrop) in rheumatoid arthritis has received further substantiation. Hydroxychloroquin (Plaquenil—Winthrop) has also been found of value and it has the advantage of lower toxicity. Plaquenil is employed in an initial dose of 400-600 mg. daily and then on a maintenance dose of 200-400 mg. daily. It is available as 200 mg. tablets.

Plaquenil is also of value in cardiac arrhythmias and in lupus erythematosus. A combination of Atabrine, Aralen, and Plaquenil was recently released as Triquin (Winthrop) for use in lupus and polymorphic light eruptions. It is claimed to be more effective and better tolerated than its components given singly. Triquin tablets contain Atabrine hydrochloride 25 mg., Aralen phosphate 65 mg., and Plaquenil sulfate 50 mg.

BOOK REVIEWS

Photomicrography, Second Edition. Roy M. Allen. 441 pp. D. Van Nostrand Company, Inc., New York City, N. Y., 1958. Price: $9.00.

This thoroughly revised, enlarged, and well-illustrated book provides a simple guide to an art that has had many advances in the past several years. Included in ten chapters are: phase, interference and electron microscopy, the use of integral light sources, light field, dark field, and polarized light.

A detailed explanation of microscopic and photographic equipment is accompanied by many excellent illustrations. The use of black and white film, color film, dark room materials and techniques, copying, enlarging, and reducing with commercially available and homemade equipment is thoroughly considered.

The book is an excellent primer and guide on how to use equipment for taking microphotographs and processing them as negatives, positives, transparencies, prints, and lantern slides for the beginner as well as the professional.

BERNARD WITLIN

Mathematics and Statistics for Use in Pharmacy, Biology and Chemistry. L. Saunders and R. Fleming. 259 pp. The Pharmaceutical Press, London, 1957. Price: 27s. 6d. (Postage 1s.).

The book presents a short course in mathematics and statistics. Ten chapters are devoted to arithmetic, algebra, graphs, natural logarithms, differential calculus, higher derivatives and partial differentiation, integration, trigonometry, differential equations, and equations and sines. Five additional chapters deal with statistical methods. This is followed by thirteen appendices dealing with basic mathematical equations and tables of four-figure logarithms and anti-

logarithms. A section which provides the answers to mathematical problems is presented at the end of each of the first thirteen chapters; this is followed by an index.

The book is an excellent presentation of a subject difficult to present in brief narrative form. For solving any of the problems given at the end of various chapters, one would welcome the use of an additional book for square and square root tables which are not included in this text. Although primarily designed for pharmacists and students of pharmacy, the book should be of value to practitioners and students of other applied sciences including medicine, bacteriology, biology, and chemistry.

BERNARD WITLIN

Laboratory Manual for Introduction to Pharmacy, Third Edition. H. M. Burlage, J. B. Burt, L. W. Rising, and W. J. Sheffield. xv + 271 pp. The Blakiston Division, McGraw-Hill Book Company, Inc., New York N. Y., 1956. Price: $4.50.

This manual contains thirty-five laboratory experiments dealing with many of the introductory principles and processes of laboratory pharmacy. It also contains a section containing report sheets for each of the experiments for use in recording the observed results of each experiment.

The experiments have been carefully selected and should make a worthwhile contribution to those who undertake them. Included in the experiments are studies involving the balance, weights and measures, physical properties of matter, surface tension and surface-tension phenomena, solubility, solutions, isotonic solutions, colloidal solutions, and emulsification.

This laboratory manual could serve well as a formal manual for use by students taking a course in introductory pharmacy laboratory as it has been taught for many years. The manual will have to be revised substantially if it is to have any use in the pharmacy curricula already introduced or about to be introduced in the colleges of pharmacy.

MARTIN BARR

A Guide to the Literature of Chemistry, Second Edition. E. J. Crane, A. M. Patterson, and E. B. Marr. xv + 397 pp. John Wiley and Sons, Inc., New York 16, N. Y., 1957. Price: $9.50.

The literature of chemistry is said to be the best organized, most complete, and well-indexed of all the sciences. To be able to utilize this wealth of recorded information is the subject of this book. All conceivable sources of information, such as books, journals, patents, theses, lectures, trade publications, libraries, indexes, etc., are discussed in detail. The merit and inadequacies of each of these sources of information is thoroughly pursued.

Perhaps the most interesting and important chapter, from the teaching aspect, is that devoted to "Procedure in Literature Searches," which includes ideas for systematic searching, the use of mechanical aids, record keeping, and notes.

Much information listed in the appendix is probably unobtainable from any other single source. Discontinued journals, lists of symbols and abbreviations, dealer and publisher names and addresses, etc., are easily located here.

Without doubt, every practicing chemist worthy of the name should have access to this key to the literature of chemistry.

A. R. Gennaro

Biochemical Preparations, Volume 6. C. S. Vestling, Editor-in-Chief. ix + 105 pp. John Wiley and Sons, Inc., New York 16, N. Y., 1958. Price: $5.25.

This new volume of the now familiar "Preparation" and "Syntheses" series of chemistry follows the format of the previous volumes. Included in this latest edition are nineteen tested procedures for the preparation of materials of biochemical interest. The entire gamut from enzymes, sterols, amino acids, peptides through nucleic acids is covered. A list of compounds appearing in *Organic Syntheses* thru volume 38, which are of biochemical value, is also given. The index is cumulative for the first six volumes of this series.

A. R. Gennaro

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

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